Interventions for treating slipped upper femoral epiphysis (SUFE) (Protocol)

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[Intervention Protocol]

Interventions for treating slipped upper femoral epiphysis (SUFE)

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ABSTRACT

This is the protocol for a review and there is no abstract. The objectives are as follows:

The primary objective of this review is to assess the effects of non-operative treatments such as hip spica or traction, and surgical treatments such as pinning in situ and open reduction and fixation for the treatment of slipped upper femoral epiphysis (SUFE). Secondary objectives include; assessing the effects of timing of the surgery on the outcome AVN, assessing the effects of prophylactic fixation of the contralateral unaffected side and finding predictors for development of contralateral slips in patients with SUFE.

BACKGROUND

Description of the condition

Although a rare condition, slipped upper femoral epiphysis (SUFE) is one of the most common types of paediatric and adolescent hip disorder. SUFE involves instability of the growth plate (often called the physis) at the junction between the head and neck of the thigh bone (femur) resulting in the head of the femur staying in the acetabulum and the neck slipping forward and outward. Although, the cause is poorly understood, several anatomical features and medical conditions have been implicated. The following features lead to an increase in the shear forces across the physis and can lead to SUFE (Herring 2008):

1. increased weight (> 80^{th} centile);
2. femoral retroversion (> 10º);
3. increased physis height due to widened hypertrophic zone;
4. more vertical slope of the physis; and
5. trauma.

Medical conditions associated with SUFE include endocrine disorders, renal failure osteodystrophy and previous radiation therapy (Loder 2000). About 30% of SUFE patients subsequently develop bilateral SUFE with the other hip slipping as well.

The incidence of SUFE varies with sex, age, and racial group, with an overall incidence of 10 per 100,000 children. This may be an under-estimate, as mild cases may not be diagnosed until arthritis supervenes many years later. SUFE is more common in boys (75% of cases) with the peak incidence occurring at 12 to 15 years compared to 10 to 13 years in girls. Thus, boys tend to have their slip two years older than girls (Montgomery 2009). SUFE is rarely reported after the age of 20 years (Kelsey 1970). The classical presentation is an overweight child presenting with groin, thigh or knee pain or both (referred pain, obturator nerve) and limping. There may be a history of minor trauma. The child may be able to ambulate (stable slip) or may not be able to do so even with crutches (unstable slip). If the participant can walk, and there is an external rotation of the involved limb and it is not possible to sit comfortably without keeping the leg straight (as the hip cannot bend). There is usually restriction in the range of movement of the affected hip. With increasing severity, SUFE is associated with increasing pain and disability.

Several classifications have been proposed for SUFE.

Functionally, SUFE may be classified according to weight-bearing status (Loder 1993) as:

1. stable: patient is able to ambulate and bear their weight; or
2. unstable: patient is unable to ambulate with or without crutches.

In a case series of 55 SUFEs, Loder showed that avascular necrosis (AVN) developed in 47% of unstable slips compared to none in patients with stable slips (Loder 1993). Anatomical reduction of SUFE occurred in 26 unstable slips (out of 30) and in only two of the stable slips (out of 25). Loder was not able to demonstrate an association between early reduction and the development of AVN. Table 1 provides a glossary of terms associated with slipped upper femoral epiphysis.

SUFE has been classified chronologically; relating to the onset of symptoms.

1. Preslip: patient has symptoms with no anatomical displacement of the femoral head. There may be useful radiological evidence such as widening of the physis, osteopenia of the pelvis.
2. Acute: there is an abrupt displacement through the proximal physis with symptoms and signs developing over a short period of time (< 3 weeks).
3. Chronic: patients with a chronic slipped capital femoral epiphysis present with pain in the groin, thigh, and knee that varies in duration, often ranging from months to years.
4. Acute on chronic: initially, patient has chronic symptoms, but develops acute symptoms as well following a sudden increase in the degree of slip.

Radiographical classification is based on the degree of displacement either by proportion of slip, or by the angular displacement of slip. Wilson 1965 classified slips as:

1. mild slip (grade I) where the displacement of the physis as a proportion of neck width is less than one third;
2. moderate slip (grade II), displacement is between one third and one half of neck width; or
3. severe slip (grade III) has displacement of greater than one half of neck width.

Angular displacement is measured by the Southwick angle of the slip (Southwick 1967). The angle is measured on the lateral view of the both hips. It is measured by drawing a line perpendicular to a line connecting the posterior and anterior tips of the epiphysis at the physis. The angle between the perpendicular line and the femoral shaft line is the angle. The angle is measured bilaterally. The slipped side is then subtracted from the normal side. The number calculated determines the severity which is classified as:

1. mild slip (Grade I) < 30°;
2. moderate slip (Grade II) is 30° to 50°; or
3. severe slip (Grade III) is > 50°.

In practice, most clinicians tend to use a combination of the Loder classification and one of the radiographic classifications. There is some crossover between the classifications but severe slips are more likely to be unstable (Montgomery 2009).

Most investigators agree that once a SUFE has been diagnosed, surgical treatment is indicated to prevent progression of the slip. The goal of treatment has always been to prevent additional slippage while avoiding the complications of avascular necrosis (AVN) and chondrolysis (Loder 2000). Recently, the importance of reducing the slip has been emphasised in preventing femoro-acetabular impingement (FAI) and premature osteoarthritis (OA) (Dodds 2009; Ganz 2003).

Description of the intervention

There is almost a universal consensus about the treatment of Grade I and (to a lesser extent) grade II SUFE: placing a single screw across the growth plate through a very small incision on the thigh to prevent further slip until growth plate closure. This procedure is commonly referred to as a percutaneous pinning or pinning in situ (PIS). Sometimes, more than a single screw is required to prevent further progression depending on the initial stability, severity and bone quality. Some advocate multiple smooth pins in very young affected children (less than 8 years old) to allow for growth (Staheli 2008). The screw must not be removed prior to physeal closure, otherwise progression of the slip may resume. The appropriateness of removal after physeal closure is contended. If the slip is more severe, a more involved procedure or corrective surgery may be necessary. Pinning in situ may not be physically possible without reducing the slip, hence the need for reduction. Forceful closed reduction of a slipped epiphysis is contraindicated due to high risk of AVN. Some advocate pinning in situ with a re-alignment procedure performed at a later date. Others recommend immediate open reduction and fixation. There are several techniques used to achieve open reduction and fixation including Dunn's osteotomy, Fish osteotomy and surgical dislocation. However, the relative effectiveness of these techniques is contested.

The timing of operation is controversial. Given the rarity of the condition, most studies that looked at the timing of surgery and outcome were underpowered. In a meta-analysis of five studies (130 unstable SUFEs where 56 were treated within 24 hours and 74 were treated after 24 hours of symptom onset), Lowndes 2009 found that the odds for developing AVN if treatment occurs within 24 hours might be halved for developing AVN when compared to later treatment, although the difference was not statistically significant (P = 0.44). Peterson 1997 showed early stabilization within 24 hours was associated with less AVN (3/42 = 7%) in comparison with those stabilized after 24 hours (10/49 = 20%). Kalogrianitis 2007 showed that AVN developed in 50% (8/16) of unstable SUFE. All but one of these SUFE were treated between 24 and 72 hours after symptom onset. Kalogrianitis 2007 recommended immediate stabilization of unstable slips presenting within 24 hours, or if not possible, delaying the operation for at least one week. However, consistent with lack of power to inform the issue of timing, Loder 1993 noted more AVN in patients treated within 48 hours compared to those treated after 48 hours (7/8 versus 7/21).

Prophylactic pinning of the normal contra-lateral side is also controversial. The quoted risk of contralateral slip varies from 18 to 60%. Prophylactic PIS is not free of risk which should be weighed against the benefit. Both proponents and opponents have some evidence to support their views (Jerre 1994; Herring 2008). Stasikelis 1996 performed a retrospective review of 50 children who presented with unilateral SUFE to determine parameters that predict the later development of a contralateral slip. They found the modified Oxford bone age (a measure of physiological maturity) strongly correlated with the risk of development of a contralateral slip; contralateral slip developed in 85% of patients with a score of 16, in 11% of patients with a score of 21, and in no patients with a score of 22 or more. The modified Oxford bone age is based on appearance and fusion of the iliac apophysis, femoral capital physis, and greater and lesser trochanters.

We adopted a pragmatic approach for contralateral pinning where the following factors play a role in decision making:

1. age of the child (< 10 years is associated with a higher risk of bilaterality);
2. the aetiology of the slip (renal osteodystrophy and endocrine disorders have a high incidence of bilaterality);
3. the compliance of the child and family; and
4. the nature of current slip (Severe slip occurred over a very short period of time with no prodromal symptoms may justify pinning the other side).

How the intervention might work

The goal of treatment is to prevent additional slippage by providing mechanical stability using screws or pins while avoiding the complications of avascular necrosis (AVN) and chondrolysis. AVN and chondrolysis are the most important and robust outcomes of SUFE treatment. They are readily identifiable and their development is a good indicator for a bad outcome. However, the opposite is not true.

The potential for further slip continues until physeal closure (ossification of the growth plate). After physeal healing, there may be a residual displacement which impair function and quality of life, whilst the patient is still young. A realignment procedure (such as trochanteric, subtrochanteric or femoral neck osteotomy) may improve function in these patients. In older patients with established degenerative changes, total hip replacement may be indicated. Reducing the slip provides extra stability, improved function and may prevent or reduce long term complications; provided short term complications such as AVN and chondrolysis do not occur.

Why it is important to do this review

The management of SUFE is controversial and still evolving with advancing knowledge, surgical skills and expertise. The infrequency of cases, the various classifications in use, the various treatment options, and lack of robust evidence for outcomes, has resulted in the lack of clear, evidence-based recommendations for treatment (Montgomery 2009). This has led to significant variations in clinical practice threatening possible optimum care for this group of patients. There have been a few published attempts (Loder 2000; Lowndes 2009; Wright 2009) to produce recommendations to treat SUFE (Loder 2000; Lowndes 2009; Wright 2009). However, these attempts lacked a rigorous and structured

approach of critically appraising the available evidence, which is the purpose of this review.

OBJECTIVES

The primary objective of this review is to assess the effects of non-operative treatments such as hip spica or traction, and surgical treatments such as pinning in situ and open reduction and fixation for the treatment of slipped upper femoral epiphysis (SUFE). Secondary objectives include; assessing the effects of timing of the surgery on the outcome AVN, assessing the effects of prophylactic fixation of the contralateral unaffected side and finding predictors for development of contralateral slips in patients with SUFE.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised controlled trials (RCTs) or controlled clinical trials (CCTs) which investigate interventions (listed below) for the treatment of SUFE will be considered for inclusion. Inclusion will be limited to randomised designs if adequately informative. If necessary inclusion will be extended first to other controlled clinical trial designs and second to other controlled observational designs such as controlled before-after studies (CBAs) and interrupted time series (ITS). The primary outcome (AVN) usually becomes apparent within a year and is rarely reported after one year. Thus we will exclude any study that does not have this minimum one year follow-up. Uncontrolled studies such as case series and case reports will be excluded.

Types of participants

Children (under 20 years old) with a confirmed diagnosis of SUFE will be considered for inclusion. Children undergoing revision for previously failed treatment will be excluded.

Types of interventions

Three interventions for treating SUFE will be considered; non-operative treatments such as hip spica or traction, pinning in situ and open reduction and fixation. With a few exceptions, non-operative treatments have become obsolete as a sole treatment for SUFE. However, traction may be used temporarily before operative treatment and hip spica may be used to augment unreliable fixation. Studies of patients who underwent such a combined treatment will be analysed as a subgroup provided sufficient numbers are available. Interventions will be assessed as follows.

1. Non-operative treatments such as hip spica or tractions versus operative treatment.
2. Pinning in situ versus open reduction of the slip.
3. Comparing different open reduction techniques of the slip such as (Dunn's, Fish and surgical dislocation).
4. Prophylactic fixation of the other (unaffected) hip versus no prophylactic fixation.

Types of outcome measures

Major outcomes

1. Avascular necrosis of the head of the femur (as binary outcome).
2. Chondrolysis (as binary outcome).

Minor outcomes

1. Complications such as infection, nerve palsy, femoro-acetabular impingement or secondary osteoarthritis.
2. Re-operation rate and the need for future salvage operations.
3. Survival of the implant until there is no risk of further slip.
4. Health related quality of life measures and functional measures with validated instruments (e.g. Oxford hip score Murray 2007, EuroQol Brooks 1996).
5. Pain (e.g. using visual analogue scale).
6. Other validated clinician, parent or patient based performance scores.

The following outcomes will be included in the summary of findings table for each intervention considered:

1. Avascular necrosis of the femoral head;
2. Chondrolysis;
3. Re-operation rate;
4. Infection;
5. Neurovascular damage;
6. Health related quality of life measures and functional measures with validated instruments; and
7. Pain score.

Search methods for identification of studies

Electronic searches

We will search the Cochrane Bone, Joint and Muscle Trauma Review Group Specialised Register, the Cochrane Central Register of Controlled Trials (The Cochrane Library, current issue), MEDLINE (1966 to present), EMBASE (1980 to present), CINAHL

(1982 to present), and Science Citation Index (ISI Web of Science 1987 to present).

Appendix 1 summarises the search strategy for MEDLINE, which will be modified for the other databases.

Searching other resources

We will search the following web sites to identify additional unpublished and ongoing studies: Current Controlled Trials (http://www.controlled-trials.com/), Centre Watch (www.centerwatch.com), TrialsCentral (http://www.trialscentral.org/), the UK Clinical Research Network: Portfolio Database (http://public.ukcrn.org.uk/search/), and SUMSearch (http://sumsearch.org/).

We will hand search the Journal of Bone and Joint Surgery - British Volume (http://proceedings.jbjs.org.uk/), the Journal of Bone and Joint Surgery - American Volume (http://www.jbjs.org/), and the American Academy of Orthopaedic Surgeons (www.aaos.org) for any relevant publications.

The bibliographies of retrieved trials and other relevant publications, including reviews and meta-analyses, will be cross referenced to identify additional studies.

Data collection and analysis

Selection of studies

Two authors (JB & KT) will independently apply the search strategy to identify citations. Article titles and abstracts will be reviewed independently (by JB & KT). Where a study appears eligible or further clarity is required, the full article will be obtained for further scrutiny. The two authors will independently assess each full study report to see whether it meets the inclusion criteria. Where necessary, authors will be contacted for more information and clarification of data. If there is still a disagreement regarding inclusion, senior authors (SA, AN, RM and JM) will be consulted and when no consensus is reached, the study will be excluded.

Data extraction and management

Data will be extracted independently by two authors (JA & KT) using a piloted form (See Table 2). Discrepancies will be resolved through discussion. The names of the authors and the institutes will not be masked.

Assessment of risk of bias in included studies

Two authors (SA, KT) will independently assess the risk of bias in included studies using the Cochrane risk of bias tool (Higgins 2011). This instrument addresses seven specific domains including sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective outcome reporting and other potential sources of bias. Other potential sources of bias include inappropriate administration of an intervention (or co-intervention), contamination, selective reporting of subgroups and fraud (See Table 3). Each domain will be assessed as 'low risk' of bias, 'high risk' of bias or 'unclear risk' of bias. Disagreement will be resolved by consensus. Unclear risk of bias will be assigned if consensus is not reached. The Newcastle-Ottawa Scale (Wells 2012) will be used to assess the methodological quality of non-randomised studies (NRS) (See Table 4 and Table 5).

Measures of treatment effect

Continuous data will be recorded as mean, standard deviation (SD) and group size for each trial arm, with the treatment effect being reported as the mean difference (MD) with corresponding 95% confidence interval (95% CI). We will use the mean difference to summarise trial findings if outcomes are measured in the same way between trials. We will use the standardised mean difference (SMD) to compare trials that measure the same outcome (construct), but use different scales. Dichotomous data will be expressed as proportions or risks, with the treatment effect reported as a risk ratio (RR) with 95% CI. Statistical significance will be set at $P < 0.05$.

Unit of analysis issues

For cluster randomised trials and body-part randomisation designs, we will conduct the analysis at the same level as the allocation, using a summary measurement for each cluster (or the participants).

Dealing with missing data

Missing data will be sought from the original authors. Where this is not possible or data is missing through loss to follow-up, intention-to-treat principles will be used. No attempt at imputation will be made.

Assessment of heterogeneity

Heterogeneity will be identified by visual inspection of the forest and funnel plots and quantified using the I^2 statistic. Heterogeneity manifests itself in poor overlap of confidence intervals in a forest plot, by scatter beyond 95% confidence bounds in a funnel plot and by scatter beyond the ± 2 lines in a Galbraith plot (Anzures-Cabrera 2010; Bax 2009). We will carry out statistical pooling on groups of studies which are considered to be sufficiently similar. Where heterogeneity is absent or low (I^2 = 0% to 25%) we will use a fixed-effect model; if there is evidence of heterogeneity (I^2 more than 25%), we will use a random-effects model. If heterogeneity is very high (I^2 over 75%), this will be explored by checking the data accuracy, and by performing subgroup analysis or sensitivity analysis (Higgins 2003). If there is considerable

variation in results, and particularly if there is inconsistency in the direction of effect, we will not quote an average value for the intervention effect (Deeks 2011).

Assessment of reporting biases

If sufficient studies (10 or more) are identified, we plan to assess potential publication bias using a funnel plot (Sterne 2001).

Data synthesis

Results of comparable groups of trials will be pooled using a fixed-effect model. A pooled RR and 95% CI will be calculated for dichotomous outcomes. A pooled MD and 95% CI will be calculated for continuous outcomes. Where findings are substantially heterogenous (I^2 over 75%), they will not be pooled but will be summarised in a table.

Subgroup analysis and investigation of heterogeneity

When data allow, we will perform sub-group analysis to investigate the following.

1. Timing of surgery (immediate, within 48 hours, after 48 hours).
2. Mode of fixation (a single screw, multiple screws, multiple pins, partially threaded or fully threaded screws).
3. Grade of the slip (mild, moderate or severe)
4. Stability of the slip as per Loder's definition (Stable or Unstable)
5. Prophylactic fixation of the other (unaffected) hip.
6. Use of bone graft.
7. Gender.
8. Age (younger and older than 8 years of age (Staheli 2008).

Sensitivity analysis

Where appropriate, we plan sensitivity analyses investigating the effects of allocation concealment, assessor blinding, loss to follow-up and publication status.

Summary of findings table

The GRADE approach (Schünemann 2011), will be used to assess the quality of the body of evidence supporting each outcome (Schünemann 2011). A 'Summary of findings' table will be produced using the GRADE-pro software. This table will provide key information regarding the quality of the evidence, the magnitude of effect of the interventions examined, and the sum of available data for the main outcomes. The overall quality of the evidence supporting each outcome will be graded as:

1. **High quality:** Further research is very unlikely to change our confidence in the estimate of effect.
2. **Moderate quality:** Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
3. **Low quality:** Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
4. **Very low quality:** We are very uncertain about the estimate.

The following outcomes will be included in the 'Summary of findings' tables:

1. AVN;
2. Chondrolysis;
3. Re-operation rate;
4. Infection rate;
5. Neurovascular damage;
6. Health related quality of life measures and functional measures with validated instruments; and
7. Pain score.

In addition to the absolute and relative magnitude of effect provided in the 'Summary of findings' table, the number needed to treat (NNT) will be calculated from the control group event rate (unless the population event rate is known) and the risk ratio using the Visual RxNNT calculator (Cates 2012). For continuous outcomes, the NNT will be calculated using the Wells calculator software available at the CMSG editorial office. The minimal clinically important difference (MCID) for each outcome will be determined for input into the calculator.

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* *Indicates the major publication for the study*

ADDITIONAL TABLES

Table 1. Glossary of Terms

Terms	Definition
AVN	Avascular necrosis; the death of the bone secondary to the loss of blood supply
Chondrolysis	The gradual thinning and subsequent loss of the articular cartilage
Prodromal symptom	Prodrome is an early symptom (or set of symptoms) that might indicate the start of a disease before more specific symptoms occur
Retroversion	Pointing backward relative to the front of the body. Normally, the femoral neck is pointing 15º forward
SUFE or SCFE	These are the two most common abbreviations for the slipped upper (or capital) femoral epiphysis

Table 2. Data extraction sheet

Study ID			
Action			
Methods Allocation: Blindness: Duration:			
Participants			
	Group 1	Group 2	Group 3
Age			
Sex			

Table 2. Data extraction sheet (*Continued*)

Side	Left			
	Right			
	Bilateral			
Duration of symptoms				
Time to surgery				
Severity	I			
	II			
	III			
Stability	Stable			
	Unstable			
Interventions 1. 2. 3.				
Outcomes		Group 1	Group 2	Group 3
AVN				
Chondrolysis				
Re-operation				
Infection				
Pain				
NV damage				
Femoro acetabular impingement				
Osteoarthritis				
Health related quality of life measures				
Functional measures				

Table 2. Data extraction sheet (*Continued*)

Others				
Range of motions	Flexion			
	Extension			
	Abduction			
	Adduction			
	Internal rotation			
	External rotation			
Contralateral involvement	Number			
	Time			
	Severity			
	Stability			
	Intervention			
	Other			
Notes				

Table 3. Risk of Bias Assessment Tool for Randomised Controlled Studies

Domain	**Risk**	**Review authors' judgement examples**
Random sequence generation	Low	Using a computer random number generator
	High	Sequence generated by odd or even date of birth. Allocation by judgement of the clinician
	Unclear	Insufficient information about the sequence generation process to permit judgement of "Low risk" or "High risk"
Allocation concealment	Low	Central allocation (including telephone, web-based and pharmacy-controlled randomisation)
	High	Allocation using case record number
	Unclear	Insufficient information to permit judgement of "Low risk" or "High risk"

Table 3. Risk of Bias Assessment Tool for Randomised Controlled Studies (*Continued*)

Blinding of participants and personnel	Low	Blinding of participants and key study personnel ensured, and unlikely that the blinding could have been broken
	High	No blinding or incomplete blinding, and the outcome is likely to be influenced by lack of blinding
	Unclear	The study did not address this outcome
Blinding of outcome assessment	Low	Blinding of outcome assessment ensured, and unlikely that the blinding could have been broken
	High	No blinding of outcome assessment, and the outcome measurement is likely to be influenced by lack of blinding
	Unclear	Insufficient information to permit judgement of "Low risk" or "High risk"
Incomplete outcome data	Low	No missing outcome data or missing outcome data balanced in numbers across intervention groups, with similar reasons for missing data across groups
	High	"As-treated" analysis done with substantial departure of the intervention received from that assigned at randomisation
	Unclear	Insufficient reporting of attrition/exclusions to permit judgement of "Low risk" or "High risk"
Selective reporting	Low	The study protocol is available and all of the study's pre-specified (primary and secondary) outcomes that are of interest in the review have been reported in the pre-specified way
	High	Not all of the study's pre-specified primary outcomes have been reported
	Unclear	Insufficient information to permit judgement of "Low risk" or "High risk"
Other sources of bias.	Low	The study appears to be free of other sources of bias
	High	Had a potential source of bias related to the specific study design used
	Unclear	Insufficient information to assess whether an important risk of bias exists

Table 4. Risk of Bias Assessment Tool for Cohort Studies

Domain	Items	Maximum Number of stars	Notes
Selection	1) Representativeness of the exposed cohort	1	Maximum possible stars is 4

Table 4. Risk of Bias Assessment Tool for Cohort Studies (*Continued*)

	2) Selection of the non exposed cohort	1	
	3) Ascertainment of exposure	1	
	4) Demonstration that outcome of interest was not present at start of study	1	
Comparability	Comparability of cohorts on the basis of the design or analysis	2	Maximum possible stars is 2
Outcome	1) Assessment of outcome	1	Maximum possible stars is 3
	2) Was follow-up long enough for outcomes to occur	1	
	3) Adequacy of follow up of cohorts	1	

Table 5. Risk of Bias Assessment Tool for Case-Control Studies

Domain	Items	Maximum Number of stars	Notes
Selection	1) Is the case definition adequate?	1	Maximum possible stars is 4
	2) Representativeness of the cases	1	
	3) Selection of Controls	1	
	4) Definition of Controls	1	
Comparability	Comparability of cohorts on the basis of the design or analysis	2	Maximum possible stars is 2
Exposure	1) Ascertainment of exposure	1	Maximum possible stars is 3
	2) Same method of ascertainment for cases and controls	1	
	3) Non-Response rate	1	

APPENDICES

Appendix 1. Search strategies

1 Epiphyses, Slipped/
2 (slipped adj3 upper adj3 femoral adj3 epiphysis).tw.
3 Femur Head/ab, pa, su [Abnormalities, Pathology, Surgery]
4 exp Femur Neck/ab, pa, su [Abnormalities, Pathology, Surgery]
5 SUFE.tw.
6 (slipped adj3 epiphyses).tw.
7 exp Slipped Capital Femoral Epiphyses/
8 SCFE.mp. or SCUFE.tw. [mp=title, abstract, original title, name of substance word, subject heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]
9 or/1-8
10 randomized controlled trial.pt.
11 controlled clinical trial.pt.
12 randomized.ab.
13 placebo.ab.
14 drug therapy.fs.
15 randomly.ab.
16 trial.ab.
17 groups.ab.
18 or/10-17
19 exp animals/ not humans.sh.
20 18 not 19
21 9 and 20

CONTRIBUTIONS OF AUTHORS

Author	Contributions
Sattar Alshryda	Contact author; taking primary responsibility for the development of the proposal and ensuring the continuity of the review once published
Kai Tsang	Literature search and data extraction. Translation of the Chinese literature
Jalal Al-Shryda	Literature search and data extraction. Translation of the German literature
John Blenkinsopp	Designed the search strategy and edited the search methods
Akinwanda Adedapo	Content expert
Richard Montgomery	Content expert
James Mason	Edited the protocol; advised on methodology, interpretation and protocol content. Approved the final protocol prior to submission

DECLARATIONS OF INTEREST

None Known